REMARKS

Claims 1-107 are currently pending in the application. Claims 43-50, 52, 53 and 55-107 are withdrawn from consideration. Claims 1, 2, 6, 10-15, 20, 29, and 34 are amended. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

Applicant notes that claims 2, 10-14, 16, 24-28, 30 and 38-42 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicant believes the amendments to the claims obviates the objection, and respectfully requests allowance of these claims.

New Matter Objection under 35 U.S.C. § 132

The Examiner has objected to the Preliminary Amendment filed October 18, 2002 for allegedly adding new matter into the disclosure because some of the amino acid sequences of the polypeptide fragments, which the Examiner refers to as "subsequences," correspond to the amended SEQ ID NO:10 of full-length Tumstatin while others do not. Specifically, the Examiner notes an inconsistency in the amendments to the specification and Table 1 (page 47), in which the numbering of terminal residues of two fragments contain apparent errors. The Applicant thanks the Examiner for noting the discrepancies, and has amended the specification accordingly. The Applicant has amended the specification and Table 1 to reflect the correct amino acid sequences of two Tum-5 mutants, Tumstatin-44-131 and Tum-5-125. The Applicant believes that these amendments obviate the Examiner's objection, and respectfully requests that it be withdrawn. Support for these amendments can be found in Applicant's Preliminary Amendment filed October 18, 2002.

The Applicant notes the Examiner's statement that "Applicant contends that only T1 has changed, as it originally was presented as beginning with that proline which has been removed with the amendment. However, as seen in the table above several sequences have been changed with the amendment" (Office Action page 3, last full paragraph). Applicant wishes to clarify that while the **numbering** of the specific residues that reflect the ends of the various Tumstatin

fragments have been amended to correspond to the correct amino acid sequence of the full-length Tumstatin protein (i.e., without the N'-terminal proline), only two of the **actual sequences** of the fragments have been amended. The Examiner has noted one of these fragments, T1, which was 20 amino acids in length including the N'-terminal proline residue and as corrected (i.e., without the proline) is now 19 amino acids in length. Applicant also notes that the length of the Tumstatin 334 fragment has also changed, since the start residue is now properly identified as amino acid residue 125, rather than residue 126 (which inadvertently included an initial proline). Applicant apologizes for any confusion caused by the wording of the statement in the Preliminary Amendment.

The Enablement Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1, 3-9, 15, 17-23, 29, 31-37, 51 and 54 have been rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Office Action states at page 4, line 25, through page 5, line 7:

> The specification fails to enable a person of skill in the art to use any fragment derived from Tumstatin to inhibit tumor growth, angiogenesis or protein synthesis in endothelial cells because claim 1 reads on any fragment of Tumstatin molecule. The specification offers no guidance as to what particular fragment, other an SEQ ID NO:37 and the mutated fragments 38-42, are required to ensure the induction of tumor growth inhibition, angiogenesis inhibition, and protein synthesis in endothelial cells. A myriad of fragments is encompassed by the claims.
>
> Applicant is relying upon certain biological activities and the disclosure of a single species to support an entire genus. The claims as written encompass a broad genus of fragments with an unlimited number of possibilities with regard to the length of the polypeptide sequence. Further, the enablement issues of making the protein still remain because the specification does not teach and provide sufficient guidance as to which amino acid of SEQ ID NO:10 would have been altered such that the resultant fragment would have retained the function of inhibiting the tumor growth, angiogenesis and protein synthesis in endothelial cells. In addition, fragments derived from SEQ ID NO:10 provide a range of activities, not all [of] which are necessarily predictive of inhibited ability of tumor growth, angiogenesis and protein synthesis in endothelial cells.

Although not acquiescing to the rejection, Applicant has amended claims 1, 6, 15, 20, 29, and 34 to recite a Tumstatin fragment comprising amino acid residues 77-95 of SEQ ID NO:10 (full length Tumstatin). The present invention is based, in part, on Applicant's discovery that

deletion mutants of Tumstatin comprising as few as 19 amino acids have the surprising ability to inhibit tumor growth (see, e.g., pages 51-62, and Examples 54-59). Moreover, and importantly, Applicant discovered the *active site* of the Tumstatin molecule responsible for the anti-tumor activity, namely amino acid residues 77-95. Thus, any Tumstatin fragment comprising the recited active site sequence would be expected to have the claimed anti-tumor properties. In fact, as evidenced throughout the application, all of the truncated Tumstatin polypeptides comprising the active site sequence have the ability to inhibit tumor growth. Thus, the present claims are directed to the exemplified deletion mutants comprising the active site sequence (represented by SEQ ID Nos:37-42), namely fragments T7, T7-mutant, T8, T8-3, TP3, and P2, and specified mutants thereof. The specification describes the activity of each of these polypeptides on pages 51-62. The specification states, for example, on page 52, line 22, through page 53, line 13:

> In *in vivo* mouse tumor models, peptide T8 showed no toxicity, and inhibited tumor growth in MDAMB-435 orthotopic human breast tumor xenografts. Inhibition was over 28% at daily dosages of 1 mg per kg body weight, and nearly 49% at 2.5 mg per kg. Interestingly, at a daily dosage of 5 mg per kg, the inhibition was only 31%, but when the same dosage (5 mg per kg) was administered twice a week, the inhibition was over 41%. In the same tumor model, peptide TP3 showed over 30% inhibition when 1 mg per kg was administered daily, and 50% inhibition at 1 mg per kg daily. In another experiment, T8 and T8-3 inhibited tumor growth by 50.5% and 41.9%, respectively, when administered at 5 mg per kg, and T8-3 was ineffective at 1 mg per kg. Peptide P2 inhibited tumor growth in this cancer model by 26.4% at 1 mg per kg, and 15.9% at 5 mg per kg.
>
> In a PC3 human prostate tumor xenograft model, where peptides T7, T8, TP3, and control scrambled peptide SP1 and SP2 were administered daily, T8, T7 and TP3 at 5 mg per kg inhibited PC3 tumor growth by 45%, 66.8% and 53.2%, respectively. SP1 and SP2 inhibited growth by 31.7 and 18.7%. When administered at 5 mg per kg once a week, T8 inhibited tumor growth by 39.5%, but only 8.1% when administered twice a week, thus mirroring the results in the MDAMB-435 model. In another experiment, both the T8 and T8-3 peptides inhibited tumor growth by 35.4% at dosages of 5 mg per kg, showing that the cysteines at positions 80 and 86 do not provide a secondary structure that is required for this biological activity. P2 proved to be more effective at lower doses in the PC3 model as well as the MDAMB-435 model, inhibiting tumor growth by 31.6% and only 15.9% at 1 and 5 mg per kg, respectively.

Thus, contrary to the Examiner's statements, the Applicant is ***not*** "relying upon certain biological activities and the disclosure of a *single species* to support an entire genus." Nor do the "claims as written encompass a broad genus of fragments with an unlimited number of possibilities with regard to the length of the polypeptide sequence." Each of the amended claims recite Tumstatin fragments comprising a defined amino acid sequence.

With respect to amended claims 6, 20, and 34, the specification describes the formula for producing a generic active peptide based on the Tumstatin sequence (SEQ ID NO:10) at page 62, line 11, through page 63, line 2:

> Such a fragment can also be based on the following formula for producing a generic active peptide based on the Tumstatin sequence. The Tumstatin sequence from amino acid 60 through 100 is provided below, aligned with active Tumstatin peptides. Residues in common across the sequences are shown in capital letters.

> Such a fragment can also be based on the following formula for producing a generic active peptide based on the Tumsatin sequence. The Tumstatin sequence from amino acid 60 through 100 is provided below, aligned with active Tumstatin peptides. Residues in common across the sequences are shown in capital letters.

```
            60    65    70    75    80    85    90    95  100
Tumstatin:  qdlgtlgsclqrfttmpfLFcNVNdVcNFasrndysywlst
T3                      lqrfttmpfLFcNVNdVcNF
T7                           tmpfLFcNVNdVcNFasrndysywl
T8                      kqrfttmpfLFcNVNdVcNFasrndys
T8-3                    kqrfttmpfLFsNVNdVsNFasrndys
Tp3                           kLFcNVNcVcNFasrndys
P2                      kqrfttmpfLFdNVNdVdNFasrndys
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Generic                    xLFxNVNxVxNF

                           f  c   d c

                           k  s   c s

                              d     d
```

One can therefore create peptides based on this formula and test them for [biological] properties as described herein. For instance, one can make a peptide with the sequence of amino acid F or K, followed by LF, followed by C or S or D, followed by NVN, followed by D or C, then V, then C or S or D, and ending in NF. A total of **only 36 different peptides** can be produced with this formula, a number easily tested by the assays described herein. [Emphasis added]

One can therefore create peptides based on this formula and test them for anti-angiogenic properties as described herein. For instance, one can make a peptide with the sequence of amino acid F or K, followed by LF, followed by C or S or D, followed by NVN, followed by D or C, then V, then C or S or D, and ending in NF. A total of only 36 different peptides can be produced with this formula, a number easily tested by the assays described herein.

Applicant respectfully submits that 36 polypeptides are not a "myriad," but rather is a reasonable number of species based on the exemplary mutant polypeptides shown to retain tumor inhibitory activity.

It is well known that tumor growth occurs by perfusion of blood through the tumor, as well as by paracrine stimulation of tumor cells by several growth factors and matrix proteins produced by the new capillary endothelium (see, e.g., Folkman, J., *Nat. Med.* (1995) 1:27-31). Thus, because the Tumstatin fragments of the present invention have been shown to inhibit tumor growth in both mouse tumor models and tumor xenograft models, one of skill in the art would expect the claimed polypeptides to inhibit angiogenesis and protein synthesis in endothelial cells, as required by claims 15-28 and 29-42, 51, and 54, respectively.

Finally, Applicant note that both reduced and alkylated Tumstatin, as well as a Tumstatin fragment, had similar anti-angiogenic activity as their untreated counterparts. See Example 43. The specification states at page 160, lines 2-6 that:

> Reduced and alkylated Tumstatin and Tumstatin-45-132 exhibited effects similar to that of non-treated Tumstatin and Tumstatin-45-132 in decreasing cell viability of C-PAE cells. The anti-angiogenic effects of Tumstatin and Tumstatin-45-132 are therefore not dependent on their conformation as derived from disulfide bonds between cysteine residues.

Thus, because the anti-angiogenic activities of are dependent on amino sequence (i.e., the active site sequence) and not conformation, one of skill in the art would expect the treated polypeptides, as recited in claims 3-5, 17-19, and 31-33, to have tumor inhibitory properties similar to their untreated counterparts.

Applicant believes that the above-discussed amendments and arguments obviate the enablement rejection of claims 1, 3-9, 15, 17-23, 29, 31-37, 51 and 54 under 35 U.S.C. § 112, first paragraph, and respectfully request reconsideration and withdrawal of the rejection.

The Written Description Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1, 3-9, 15, 17-23, 29, 31-37, 51 and 54 have been rejected under 35 U.S.C. § 112, first paragraph, for failure to comply with the written description requirement. The Office Action states that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The rejection is based on the premise that while the fragments having the amino acid sequences of SEQ ID Nos:37-42 have anti-tumor activity, not all of the fragments encompassed by claim 1 will necessarily have this activity. The Office Action states at page 6, lines 9-14, that:

> Applicant has disclosed only amino acid of SEQ ID NO:37 to have the claimed activity and the mutants of SEQ IDNOs:38-42; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a

representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method.

As discussed above, Applicant discovered that deletion mutants of Tumstatin (SEQ ID NO:10) comprising as few as 19 amino acids have the surprising ability to inhibit tumor growth (see, e.g., pages 51-62) and Examples. Moreover, and importantly, Applicant discovered the *active site* of the Tumstatin mutant responsible for the anti-tumor activity, namely amino acid residues 77-95 of SEQ ID NO:10. Thus, any polypeptide comprising the recited active site sequence would be expected to have the claimed anti-tumor activity.

Although not acquiescing to this rejection, Applicant has rewritten claims 1, 6, 15, 20, 29 and 34 to specifically recite the structure responsible for the surprising biological activity of Tumstatin fragments, i.e., the active site sequence, amino acids 77-95 of SEQ ID NO:10.

The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date, applicant was in possession of the claimed invention. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patent" such as by the disclosure of drawings or structural information that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Electronics, Inc.*, 48 U.S.P.Q.2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 43 U.S.P.Q.2d 1398, 1405 (Fed. Cir. 1997) ("written description of an invention involving a chemical genus . . . 'requires a precise definition, such as by structure, formula, [or] chemical name"). As discussed above, Applicant has provided the "distinguishing identifying characteristics" or structural features common to the claimed polypeptides having

anti-angiogenic activity. The specification discloses the structure-function relationship responsible for this unexpected property, and the claims as amended recite the common structural feature (i.e., amino acids 77-95 of SEQ ID NO:10) associated with the surprising anti-tumor activity.

Moreover, a recent Federal Circuit decision (*In re Wallach*, 2004 WL 1780989, decided August 11, 2004) further supports the conclusion that all of the pending claims, including claims 6, 20, and 34, directed to a generic active polypeptide based on the Tumstatin sequence (SEQ ID NO:10), satisfies the written description requirement under 35 U.S.C. 112, first paragraph. The written description requirement is satisfied where, as here, the specification provides a representative description of the structural and functional properties of the claimed invention. The Applicant in *Wallach* attempted to patent an isolated DNA molecule by listing ten sequential amino acids, and a property of the molecule (the ability to inhibit the cytotoxic effect of TNF). However, unlike the present case, the Applicant did not describe the entire amino acid sequence (185-192 amino acids). The court held that the listing of roughly 5% of the amino acids necessary to make up the full protein is not enough to comply with the written description requirement. However, the court stated that the written description of a chemical compound (including a protein) can "in some cases" be satisfied by a functional description of the properties, but not here. The Federal Circuit clarified its earlier holding in *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316 (Fed. Cir. 2002) regarding the use of functional language to describe a genetic material (and therefore any chemical compound). Specifically, a functional description is sufficient if there exists a known structure-function relationship. Not only does the present application provide the entire amino acid sequence of the starting protein (unlike the Wallach application), but it also provides ample proof, in the form of numerous active fragments, that the active site sequence (amino acids 77-95) is the structure responsible for the anti-tumor properties. Thus, because the present application establishes a clear structure-function relationship for the recited anti-tumor activities, it satisfies the written description requirement under Section 112, first paragraph.

Applicant believes that the above-discussed amendments obviate the written description rejection of claims 1, 3-9, 15, 17-23, 29, 31-37, 51 and 54 under 35 U.S.C. § 112, first paragraph, and respectfully request reconsideration and withdrawal of the rejection.

Rejections Under 35 U.S.C. § 102

Claims 1, 6, 15, 20, 29, 34, 51 and 54 have been ejected under 35 U.S.C. § 102 as being anticipated by Kalluri et al. (*J. Biol. Chem.* (1996) 271:9062-9068), as evidenced by the provisional application 60/126,175 on page 26. The Office Action states at page 7, lines 6-14:

> Kalluri et al. teach a deletion of 26 amino acids in the triple helix and NC1 region (α3/n-26) fragment of the wild type α3(IV) chain. Kalluri et al. further teach a deletion of N-terminal triple helix 26 aa and C-terminal 36 amino acid (α3/n-26/c-36). Kalluri et al. further teach mutated fragment, α3/n-26/c-KK having a deletion of N-terminal triple helix 26 aa and substitution of last two lysines to alanines (see the entire document and page 9064 under Figure 1 in particular). While the prior art teachings may be silent as to [the claimed inhibitory activities], the product of Kalluri et al. reference is the same as the claimed product. . . .

While not acquiescing to the rejection, Applicant has amended claims 1, 6, 15, 20, and 29 (from which claims 34, 51 and 54 depend) to recite the active site sequence (amino acids 77-95), thereby distinguishing the claimed fragments from the truncated Tumstatin polypeptides disclosed in Kalluri et al. The Kalluri et al. reference neither teaches nor suggests a Tumstatin fragment having the specified amino acid sequence, nor having the recited biological activities.

Claims 1, 6, 15, 20, 29, 34, 51 and 54 have been ejected under 35 U.S.C. § 102 as being anticipated by Monboisse et al. (*J. Biol. Chem.* (1994) 269(41):25475-25482). The Office Action states that "Monboisse et al. teach four synthetic peptide fragment of NC1 domain of the α3(IV) collagen," as well as several mutated fragments. Further, "[w]hile the prior art teachings may be silent as to [the claimed inhibitory activities], the product of Monboisse et al. reference is the same as the claimed product. . . ." [Office Action, page 7, lines 29-38]

As discussed above, Applicant has amended claims 1, 6, 15, 20, and 29 (from which claims 34, 51 and 54 depend) to recite the active site sequence (amino acids 77-95), thereby distinguishing the claimed fragments from the four synthetic polypeptides disclosed in Monboisse et al. The Monboisse et al. reference neither teaches nor suggests a Tumstatin fragment having the specified amino acid sequence, nor the recited biological activities.

Applicant believes that the amendments to claims 1, 6, 15, 20 and 29 obviates the rejections under 35 U.S.C. § 102, and respectfully requests reconsideration and withdrawal of the rejections.

Rejections Under 35 U.S.C. § 103

Claims 1, 3, 6-7, 15, 17, 20-21, 29, 31 and 34-35 have been ejected under 35 U.S.C. § 103(a) as being unpatentable over Kalluri et al. (*J. Biol. Chem.* (1996) 271:9062-9068) or Monboisse et al. (*J. Biol. Chem.* (1994) 269(41):25475-25482) each in view of U.S. Patent 5,858,670. The Office Action states that:

> The teachings of Kalluri et al. and Monboisse et al. references have been discussed, supra. The claimed invention differs from the reference teachings only by the recitation that the fragment is reduced. The '670 patent teaches that a reduced peptide bond may be introduced as a dipeptide subunit. Such as molecule would be resistant to peptide bond hydrolysis, e.g., protease activity. . . . It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce the fragments taught by Kalluri et al. and Monboisse et al. as reduced fragment as taught by '670 patent. [Office Action, page 8, last three paragraphs]

As discussed above, Applicant has amended claims 1, 6, 15, 20, and 29 (from which all other rejected claims depend) to recite the active site sequence (amino acids 77-95), thereby distinguishing the claimed fragments from the truncated Tumstatin and synthetic polypeptides disclosed in Kalluri et al. and Monboisse et al., respectively. Neither of the primary references teaches or suggests a Tumstatin fragment having the specified amino acid sequence, nor the recited properties.

Claims 1, 4, 6, 8, 15, 18, 20, 22, 29, 32, 34 and 36 have been ejected under 35 U.S.C. § 103(a) as being unpatentable over Kalluri et al. (*J. Biol. Chem.* (1996) 271:9062-9068) or Monboisse et al. (*J. Biol. Chem.* (1994) 269(41):25475-25482) each in view of U.S. Patent 5,326,875. The Office Action states that:

> The teachings of Kalluri et al. and Monboisse et al. references have been discussed, supra. The claimed invention differs from the reference teachings only by the recitation that the fragment is alkylated. The `875 patent teaches that alkylated peptides can be purified by crystallization or by silica gel chromatography. Further the `875 patent teaches that protected alkylated peptides are readily soluble in acidic aqueous medium. . . . It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce the fragments taught by Kalluri et al. and Monboisse et al. as alkylated fragment as taught by the [`875] patent. [Office Action, page 9]

As discussed above, Applicant has amended claims 1, 6, 15, 20, and 29 (from which all other rejected claims depend) to recite the active site sequence (amino acids 77-95), thereby distinguishing the claimed fragments from the truncated Tumstatin polypeptides disclosed in Kalluri et al. and Monboisse et al. Neither of the primary references teaches or suggests a Tumstatin fragment having the specified amino acid sequence and activities.

Applicant believes that the foregoing amendments obviate the rejections under 35 U.S.C. § 103, and respectfully requests reconsideration and withdrawal of the rejections.

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

Date: November 5, 2004

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